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A Mathematical Model for Cholesterol Biosynthesis under Nicotine Exposure

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Abstract: In this paper, a mathematical model is considered for analyzing the impact of nicotine exposure to cholesterol biosynthesis. The dynamical model is nonlinear. Its equilibrium points are computed and conditions are provided under which a unique locally stable positive equilibrium exists. Moreover, effect of internal time delays on local stability is also investigated.

Keywords: Mathematical modeling, cholesterol biosynthesis, dynamical systems, delay equations, control theory.

1. INTRODUCTION

Each animal cell is able to synthesize cholesterol, where cholesterol is an end product after an almost linear pathway. The rate-limiting step of this network is the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, Liscum and Dahl (1992). Over accumulation of intracellular cholesterol causes cellular toxicity like intracellular cholesterol crystallization or apoptosis, Tabas (2002). High level of intracellular cholesterol depletion is also reported to be toxic and it destroys both of the membrane structure and its selective permeability, Goedeke and Fernández-Hernando (2012). That is why, the regulation of intracellular cholesterol levels have a vital impact. Indeed, cellular cholesterol homoeostasis depends on plasma cholesterol level and biosynthesis, but in this work we only concentrate on the biosynthesis mechanism since we want to understand the effect of nicotine exposure on the dynamics of this pathway. A particular approach on the dynamical modeling of cholesterol biosynthesis was given by Bhattacharya et al. (2014) and Belič et al. (2013). They examine the underlying genetic mechanisms constructing cholesterol biosynthesis in different manner. While Bhattacharya et al. (2014) focus on the response of the concerned gene to the cellular concentration of cholesterol, Belič et al. (2013) address the relation between continuous metabolic fluxes. Both of these mathematical models can be assumed as a prior idea for our modeling approach.

The major components of cholesterol biosynthetic pathway, which we need for the model derivation are shown in Figure 1. The cellular cholesterol homeostasis is directed by SREBP (sterol regulated element binding protein) family of transcription factors. SREBPs build a complex with the SREBP cleavage activating protein (SCAP) within the endoplasmic reticulum of cells. In the low level of cellular cholesterol, the SCAP−SREBP complex releases SREBP to activate $mRNA_{HMGCR}$ transcription, i.e. increases HMGCR synthesis. Otherwise, SCAP−SREBP complex remains tied, so that HMGCR translation decreases, Goedeke and Fernández-Hernando (2012). Additionally, Üçal (2010) and Sonawane et al. (2011) tested the nicotine effect on this mechanism and showed that nicotine exposure up-regulate $mRNA_{HMGCR}$ level, thus HMGCR synthesis increases. However, the underlying mechanism of this process is still unknown. Our hypothesis is that nicotine has a direct increasing effect on HMGCR and we neglect all other possible influences of nicotine to the process. So, we aim to capture the effect of nicotine intake to cholesterol regulation.

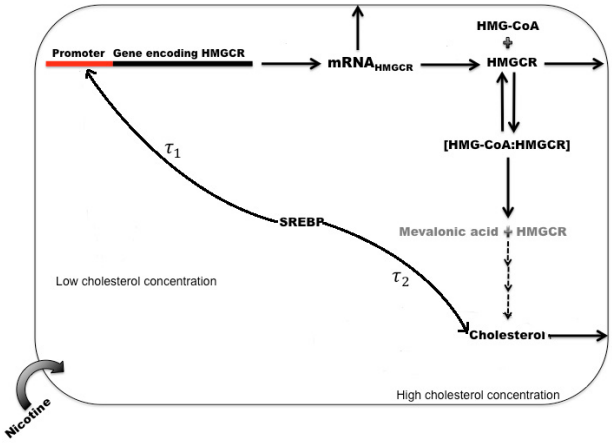

Fig. 1. Cholesterol biosynthesis pathway

In the next section a dynamical model of the process is given. In Section 3 equilibrium points are computed. Local stability analysis and effects of time delays are discussed in Section 4. A numerical example is given in Section 5 and finally concluding remarks are made in Section 6.

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2. MATHEMATICAL MODELING OF NICOTINE-CHOLESTEROL RELATION

In this paper, we focus on the effect of nicotine intake on intracellular cholesterol production. For this purpose, we propose a system of ordinary differential equations (ODEs) to describe the genetic regulation of cholesterol biosynthesis under nicotine treatment. Since HMGCR is the slowest step of the network given by Figure 1, we neglect the intermediate steps between mevalonic-acid and cholesterol. Similar biological approach is used by Bhattacharya et al. (2014) for a mathematical model describing the physiological mechanism of gene expression in cholesterol biosynthesis. We assume that SREBP feeds HMGCR concentration and binds to cholesterol at high cholesterol level. Since SREBP and HMGCR are produced by different genes and released to the same medium, we expect a time delay as shown in Figure 1. Hence we introduce time delays τ_1 and τ_2 among the relation of HMGCR and SREBP. These assumptions can be well modeled by Lotka-Volterra modeling approach introduced as follows:

$$\begin{aligned}\frac{dS(t)}{dt} &= (\alpha_1 - \beta_1 H(t-\tau_1) - \rho_1 F(t))S(t) \\ \frac{dC(t)}{dt} &= (-\alpha_3 + \beta_4 H(t) - \rho_2 F(t))C(t) \\ \frac{dH(t)}{dt} &= (-\alpha_2 + \beta_2 S(t-\tau_2) - \beta_3 C(t) + \phi N(t))H(t)\end{aligned} \tag{1}$$

where $H(t)$ denotes the concentration of HMGCR, $S(t)$ the concentration of SREBP, $C(t)$ the concentration of cholesterol and $N(t)$ the exposure of nicotine. We state the restraining relation of SREBP and cholesterol by a function $F(S, C)$. In general F is a nonlinear function, but here we take the first order approximation in the form $F(t) = \eta_1 S(t) + \eta_2 C(t)$, where η_1 and η_2 are assumed to be positive real numbers. The family of model parameters can be found in Table 1, where all variables are normalized to be non-dimensional.

Table 1. Parameter family for cholesterol biosynthesis model

α_1	S production rate
α_2	H degradation rate
α_3	C degradation rate
β_1	S consumption rate (by H)
β_2	H supplying rate (by S)
β_3	H consumption rate (by C)
β_4	C supplying rate (by H)
ρ_1, ρ_2	$S - C$ binding rate
ϕ	N triggering rate for H

3. ANALYSIS OF EQUILIBRIA

For a constant nicotine level ϕN, equilibrium points are computed from the nonlinear algebraic system of equations given below (see e.g. Hilborn (1994)):

$$\begin{aligned}\alpha_1 S - \beta_1 HS - \rho_1 FS &= 0 \\ -\alpha_3 C + \beta_4 HC - \rho_2 FC &= 0 \\ -\alpha_2 H + \beta_2 SH - \beta_3 CH + \phi NH &= 0\end{aligned} \tag{2}$$

Since we are working with a biological system we assume to have non-negative equilibria. By considering the positivity of the parameters and the variables, we have two non-negative equilibrium points given by $E_1 = (0, 0, 0)$ and $E_2 = (S^*, C^*, H^*)$ where

$$H^* = \frac{\alpha_1\rho_2 + \alpha_3\rho_1}{\beta_1\rho_2 + \beta_4\rho_1} > 0.$$

Similarly, we compute that

$$F^* = \frac{\alpha_1\beta_4 - \alpha_3\beta_1}{\beta_1\rho_2 + \beta_4\rho_1} > 0$$

assuming $\alpha_1\beta_4 > \alpha_3\beta_1$. Then, by assuming $\phi N^* > \alpha_2$ we obtain

$$\begin{bmatrix} S^* \\ C^* \end{bmatrix} = \frac{1}{\eta_1\beta_3 + \eta_2\beta_2} \begin{bmatrix} \beta_3 F^* - \eta_2(\phi N^* - \alpha_2) \\ \beta_2 F^* + \eta_1(\phi N^* - \alpha_2) \end{bmatrix}.$$

Hence, we ensure the positivity of S^* and C^* for small values of η_1 and η_2.

4. LOCAL STABILITY OF EQUILIBRIUM POINTS

For the model where time delays are ignored (i.e. $\tau_1 = \tau_2 = 0$) local stability properties of the equilibrium points are studied by computing the eigenvalues of the Jacobian matrix

$$J_E = \begin{pmatrix} J_{11} & -\rho_1\eta_2 S^* & -\beta_1 S^* \\ -\rho_2\eta_1 C^* & J_{22} & \beta_4 C^* \\ \beta_2 H^* & -\beta_3 H^* & -\alpha_2 + \beta_2 S^* - \beta_3 C^* + \phi N^* \end{pmatrix}.$$

where $J_{11} := \alpha_1 - \beta_1 H^* - \rho_1 F_S S^* - \rho_1 F^*$ and $J_{22} := -\alpha_3 + \beta_4 H^* - \rho_2 F_C C^* - \rho_2 F^*$. For the equilibrium point E_1 we have

$$J_{E_1} = \begin{pmatrix} \alpha_1 & 0 & 0 \\ 0 & -\alpha_3 & 0 \\ 0 & 0 & \phi N^* - \alpha_2 \end{pmatrix}$$

and its corresponding eigenvalues are $\lambda_1 = \alpha_1$, $\lambda_2 = -\alpha_3$ and $\lambda_3 = \phi N - \alpha_2$. Clearly, E_1 is locally unstable. On the other hand, the Jacobian matrix J_E at the equilibrium point E_2 is

$$A := J_{E_2} = \begin{pmatrix} -\rho_1\eta_1 S^* & -\rho_1\eta_2 S^* & -\beta_1 S^* \\ -\rho_2\eta_1 C^* & -\rho_2\eta_2 C^* & \beta_4 C^* \\ \beta_2 H^* & -\beta_3 H^* & 0 \end{pmatrix}.$$

For local stability we look at the roots of $det(\lambda I - A) = 0$, which is a characteristic polynomial in the form

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0.$$

The roots are in $\mathbb{C}_-$ if and only if $a_2 > 0$ and $a_1 a_2 > a_0 > 0$. From the definition of the matrix A we compute the coefficients as

$$\begin{aligned} a_0 &= (\rho_1\beta_4(\eta_1\beta_3 + \eta_2\beta_2) + \rho_2\beta_1(\eta_1\beta_3 + \eta_2\beta_2))S^*C^*H^* \\ a_1 &= (\beta_1\beta_1 S^* + \beta_3\beta_4 C^*)H^* \\ a_2 &= \rho_1\eta_1 S^* + \rho_2\eta_2 C^*. \end{aligned}$$

The assumptions for positivity of E_2 yield $a_0, a_1, a_2 > 0$. By using the above definitions and some algebraic manipulations we can show that the condition $a_1 a_2 - a_0 > 0$ is equivalent to

$$(\rho_1\beta_2 S^* - \rho_2\beta_3 C^*)(\eta_1\beta_1 S^* - \eta_2\beta_4 C^*) > 0.$$

Thus we have the following local stability conditions:

$$\left\{ \frac{S^*}{C^*} > \frac{\rho_2\beta_3}{\rho_1\beta_2} \quad \text{and} \quad \frac{S^*}{C^*} > \frac{\eta_2\beta_4}{\eta_1\beta_1} \right\}$$

or

$$\left\{ \frac{S^*}{C^*} < \frac{\rho_2\beta_3}{\rho_1\beta_2} \quad \text{and} \quad \frac{S^*}{C^*} < \frac{\eta_2\beta_4}{\eta_1\beta_1} \right\}.$$

Recall that

$$\frac{S^*}{C^*} = \frac{\beta_3 F^* - \eta_2(\phi N^* - \alpha_2)}{\beta_2 F^* - \eta_1(\phi N^* - \alpha_2)} \quad , \quad F^* = \frac{\alpha_1\beta_4 - \alpha_3\beta_1}{\beta_1\rho_2 + \beta_4\rho_1}.$$

So, if $\rho_1 > \rho_2$, $\eta_1\beta_1\beta_1 > \eta_2\beta_2\beta_4$ and $(\phi N^* - \alpha_2)$ is sufficiently small then local stability conditions for E_2 hold.

4.1 Effect of time delay

Let us consider linearization of (1) by defining small perturbations near the positive equilibrium point E_2. For this purpose we first define small perturbation around the nicotine input: $N(t) = \phi N + \delta_N(t)$. This will result in

$$\begin{aligned} S(t) &= S^* + \delta_S(t) \\ C(t) &= C^* + \delta_C(t) \\ H(t) &= H^* + \delta_H(t). \end{aligned} \tag{3}$$

From the system theory point of view we consider $\delta_N(t)$ as the input. After a simple algebraic computation it can be shown that equilibrium conditions and first order approximations lead to

$$\dot{X}(t) = A_0X(t) + A_1X(t-\tau_1) + A_2X(t-\tau_2) + BU(t)$$

where

$$X(t) = \begin{bmatrix} \delta_S(t) \\ \delta_C(t) \\ \delta_H(t) \end{bmatrix}, \qquad B = \begin{bmatrix} 0 \\ 0 \\ H^* \end{bmatrix}, \qquad U(t) = \delta_N(t)$$

and

$$A_0 = \begin{bmatrix} \eta_1\rho_1 S^* & -\eta_2\rho_1 S^* & 0 \\ -\eta_1\rho_2 C^* & -\eta_2\rho_2 C^* & -\beta_4 C^* \\ 0 & \beta_3 H^* & 0 \end{bmatrix},$$

$$A_1 = \begin{bmatrix} 0 & 0 & -\beta_1 S^* \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \quad A_2 = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ \beta_2 H^* & 0 & 0 \end{bmatrix}.$$

Note that we have $A = A_0 + A_1 + A_2$, and

$$A_1 = B_1C_1 = \begin{bmatrix} \beta_1 S^* \\ 0 \\ 0 \end{bmatrix} [0\ 0\ 1],$$

$$A_2 = B_2C_2 = \begin{bmatrix} 0 \\ 0 \\ \beta_2 H^* \end{bmatrix} [1\ 0\ 0].$$

By taking the Laplace transform of $X(t)$ for $U(t) = 0$ we have

$$\widehat{X}(s) = \left(sI - (A_0 + A_1e^{-\tau_1 s} + A_2e^{-\tau_2 s})\right)^{-1} X(0).$$

In order to determine the local stability of the delayed system we investigate the roots of

$$\chi(s) := det\left(sI - A - A_1(e^{-\tau_1 s} - 1) + A_2(e^{-\tau_2 s} - 1)\right).$$

Suppose that all roots of $det(sI - A)$ are in $\mathbb{C}_-$. Then, we discuss some special cases involving the effect of time delays on local stability.

Case 1 $\{\ \tau_1 \neq 0, \ \ \tau_2 = 0\}$

In this case we have

$$\chi(s) = det(sI - A)det(I - (sI - A)^{-1}B_1C_1(e^{-\tau_1 s} - 1)).$$

Since the non-delayed system is assumed to be locally stable, i.e. $det(sI - A)$ is a stable polynomial, by using the matrix inversion lemma, it can be shown that local stability in this case is equivalent to having the roots of the following characteristic equations in $\mathbb{C}_-$

$$1 + G_1(s)(e^{-\tau_1 s} - 1) = 0 \quad \Leftrightarrow \quad 1 + P_1(s)e^{-\tau_1 s} = 0$$

where

$$G_1(s) = C_1(sI - A)^{-1}B_1 \quad \text{and} \quad P_1 = G_1/(1 - G_1).$$

Thus, local stability of the delayed system can be determined from the Nyquist test. Also, from the above equation, since $\|e^{-\tau_1 s} - 1\|_\infty \leq 2$, a sufficient condition for delay independent stability is

$$\|G_1\|_\infty < \frac{1}{2}\ . \tag{4}$$

Case 2 $\{\tau_1 = 0, \ \ \tau_2 \neq 0\}$

Similarly to Case 1, we find that local stability is equivalent to having the roots of the following characteristic equations in $\mathbb{C}_-$

$$1 + G_2(s)(e^{-\tau_2 s} - 1) = 0 \quad \Leftrightarrow \quad 1 + P_2(s)e^{-\tau_2 s} = 0$$

where $G_2(s) = C_2(sI - A)^{-1}B_2$ and $P_2 = G_2/(1 - G_2)$.

Once the parameters of the system are fixed and the equilibrium is computed we can analyze the effect of time delays τ_1, τ_2 by using standard numerical tools for analysis of time delay systems (see e.g. Avanessoff et al. (2008) and its references). For illustration purposes, in this work we use `YALTA` for finding allowable delay values for local stability. Of course, using the same tool, one can analyze the effect of τ_1 and τ_2 , in a coupled fashion provided they are commensurate. Below we provide a numerical example.

5. NUMERICAL EXAMPLE

The numerical example given here determines allowable delay range for parameter values chosen appropriately for local stability condition of the non-delayed system. This result allows a better understanding of the model and effects of time delays. For the numerical values chosen as $N = 10$; $\phi = 1$; $\alpha_1 = .3$; $\alpha_2 = .1$; $\alpha_3 = .2$; $\beta_1 = .3$; $\beta_2 = .4$; $\beta_3 = .8$; $\beta_4 = 1.2$; $\rho_=0.1$; and $\rho_2 = 0.06$ we compute the positive equilibria H^*, C^*, S^* and investigate local stability conditions for the case $\tau_1 > 0$ and $\tau_2 = 0$. The results presented in Table 2 are obtained from `YALTA`; they indicate the conditions under which the system is locally stable around the positive equilibrium for $\tau_1 \in [0, \tau_{max})$. In particular, from Figure 2 we see that (4) is satisfied (magnitude of G_1 is less than -10dB, which is less than 0.5), so for the case $\eta_1 = 0.1$ and $\eta_2 = 0.25$ we have delay independent local stability. Figures 3 and 5 illustrate how the rightmost root of the characteristic equation $\chi(s) = 0$ vary with varying τ_1.

Table 2. τ_{max} and equilibria values for chosen η_2 values

η_1	η_2	H^*	C^*	S^*	τ_{max}
0.1	0.25	0.7778	13.6481	2.5463	∞
0.1	0.125	0.7778	18.8974	13.0449	0.9261
0.1	0.06	0.7778	23.6218	22.4936	0.6277

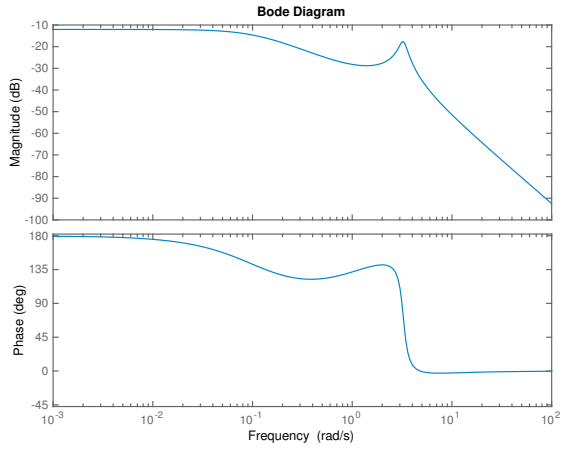

Fig. 2. Bode diagram of G_1 for $\eta_2 = 0.25$

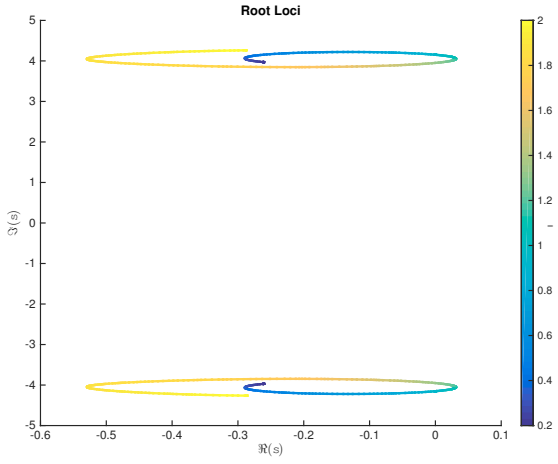

Fig. 3. Root loci with respect to $\tau_1 \in [0, 2]$ for $\eta_2 = 0.125$

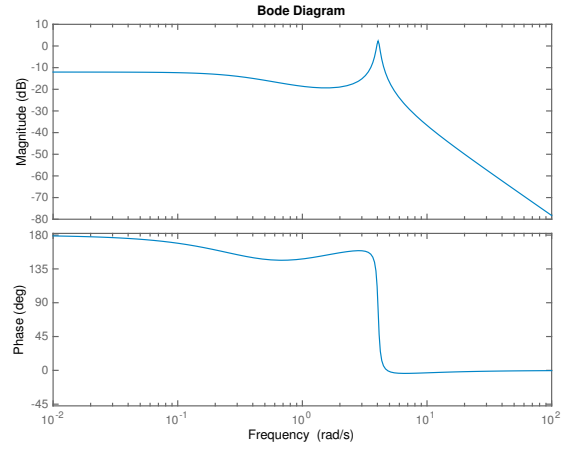

Fig. 4. Bode diagram for G_1 for $\eta_2 = 0.125$

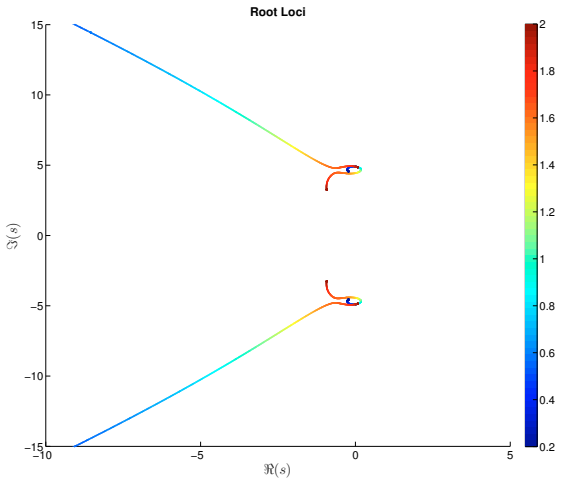

Fig. 5. Root loci with respect to $\tau_1 \in [0, 2]$ for $\eta_2 = 0.006$

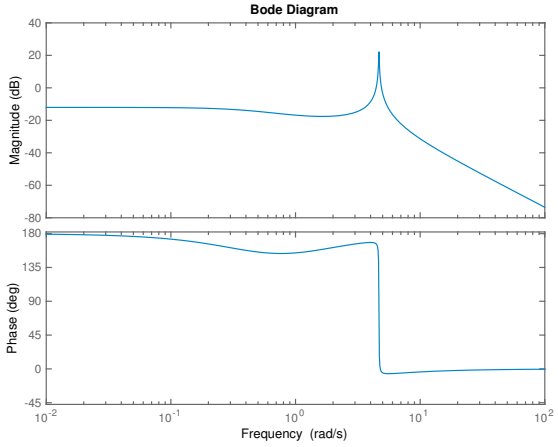

Fig. 6. Bode diagram for G_1 for $\eta_2 = 0.006$

Time-domain responses of substance concentrations are given below for two different values of τ_1; these results are obtained by using `MATLAB` Simulink tool (simulation of the nonlinear model with an initial condition in the neighborhood of the equilibrium point). Figures 7–9 show that the oscillation magnitudes around the critical delay $\tau_1 = 0.9$ are significantly larger than the oscillation magnitudes produced by the delay value $\tau_1 = 0.1$ in the stability interval.

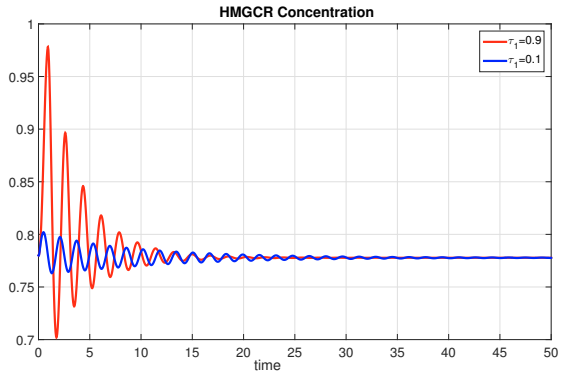

Fig. 7. Simulation results for HMGCR, for $\eta_2 = 0.125$

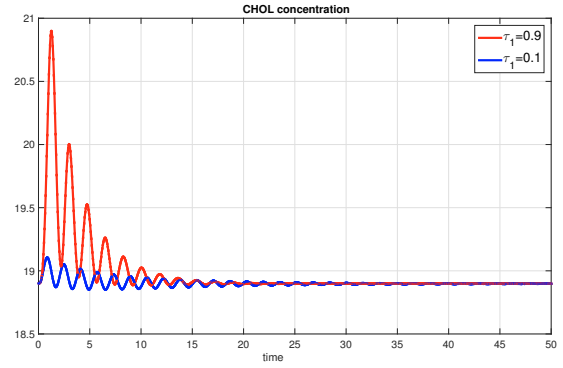

Fig. 8. Simulation results for CHOL, for $\eta_2 = 0.125$

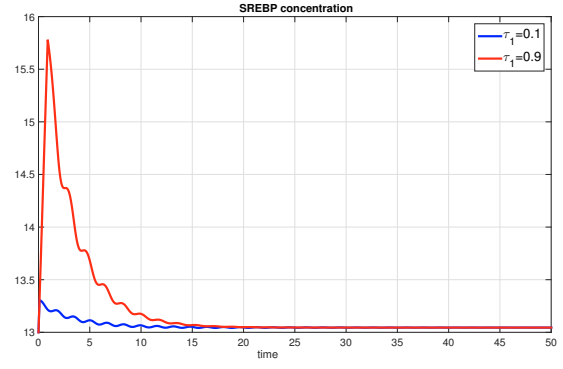

Fig. 9. Simulation results for SREBP, for $\eta_2 = 0.125$

6. CONCLUSION

In this paper we computed the equilibrium points of a model which describes the relationship with nicotine intake and cholesterol biosynthesis. The origin is locally unstable, and the positive equilibrium is locally stable depending on the parameters of the system. It is also shown that the local stability is robust to small enough delays in the model. Extensions of this work will include global stability analysis of the system considered here.

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